REMARKS

1. *History*

Claims 1-10, 12, 14-19, 59-66, 68, and 70-74 are presently pending. Claims 1-9 and 59-65 were deemed allowable in the Office Action dated May 3, 2006 ("Non-Final Office Action"). Applicants gratefully acknowledge the withdrawal of all prior rejections and the allowance of claims 1-9 and 59-65. Applicants further gratefully acknowledge the withdrawal of the rejections pursuant to 35 U.S.C. § 103. This response addresses claims 10, 12, 14-19, 66, 68, and 70-74.

The outstanding issues are addressed individually below.

2. *Claim Rejections Under 35 U.S.C. § 112, First Paragraph*

Claims 10, 12, 14-19, 66, 68, and 70-74 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter "which was not described in the specification in such a way as to enable one skilled in the art to which it pertains…to make and/or use the invention" (see Office Action, pg. 2). Specifically, the Office Action alleges that "Freshney (*Culture of Animal Cells, A Manual of Basic Techniques*, Alan R. Liss, Inc. 1983, New York, p4) teaches that the art recognizes that there are many differences between cultured cells and their counterparts *in vivo*" (see *id.* at 3, 4). The Office Action concludes that "the problems encountered in the art and the nature of unpredictability of claimed invention, the *in vivo* experimentation demonstrating that the MDR cells or neoplastic cells are detectable by modified LDL binding to surface expressed vimentin is necessary before one skilled in the art use and practice claimed invention" and therefore "one of ordinary skill in the art would forced…[to] under go [sic] an undue quantity of experimentation" (see *id.* at 4). Applicants respectfully traverse this rejection.

According to MPEP § 2164.05(b), the specification must be enabling to those of skill in the relevant art to which the claimed invention pertains at the time the application was filed. A disclosure can be enabling, while requiring experimentation to perform the claimed invention, provided that the experimentation required is not "undue." The quantity of experimentation needed to be performed by one of skill in the art is only one factor involved in determining

whether "undue experimentation" is required to make and use the invention (see MPEP § 2164.06). However, the test is not "merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" (see MPEP § 2164.06). In the chemical arts, time and difficulty of experiments are not determinative if they are merely routine (see MPEP § 2164.06).

Independent claim 10 is directed to a method for detecting a multidrug resistant cell in a patient. The method comprises administering to the patient, a vimentin binding agent operably linked to a detectable label and detecting the label. Independent claim 66 is directed to a method for detecting a neoplastic cell in a patient. The method comprises to the patient, a vimentin binding agent operably linked to a detectable label and detecting the label.

Applicants respectfully assert that the specification enables one of ordinary skill in the art to practice the claimed invention, because the specification teaches methods that can be utilized to detect multidrug resistance *in vivo*. Specifically, one of ordinary skill in the art, following the teaching in the specification, is enabled to make vimentin binding agents (*e.g.,* anti-vimentin monoclonal antibodies), label those agents (*e.g.,* radiolabel antibodies), and administer the agents to a subject (*e.g,* subcutaneous injection) (see Specification, paragraphs [0137]-[0139]; [0156]; [0161]-[0181]; [0201]-[0202]). The specification, therefore, provides significant guidance to those of ordinary skill in the art on how to practice the invention, as evidenced by the results described above. In light of this guidance, all that one of ordinary skill in the art must do to detect multidrug resistance *in vivo* is to utilize well-known techniques to detect the vimentin binding agent (see Specification, paragraphs [0127] and [0140]). Such additional experimentation is routine, requiring only limited technical know-how.

To corroborate the teachings in the specification regarding the efficacy of vimentin-directed therapy *in vivo*, ^{131}I-labeled anti-vimentin monoclonal antibodies were subcutaneously injected into athymic, BALB/C nu/nu (nude) mice carrying either human ovarian SKOV-3 xenografts or human breast MDA-MD-231 xenografts (see Georges Dec. ¶ 9 submitted herewith). These mice are well recognized animal models for human cancer. The mice were

also treated with either taxol or no chemotherapeutic drug (see Georges Dec. ¶ 9). Control mice received an isotypic injection rather than anti-vimentin antibodies (see Georges Dec. ¶ 9).

As described in the Georges Declaration submitted herewith, the size of SKOV3 human ovarian tumors decreased for mice treated with taxol and anti-vimentin antibody (see Georges Dec. ¶¶ 10 and 11). The data indicates that the anti-vimentin antibodies bound to cell-surface-expressed vimentin, thereby enhancing the effects of taxol on the cancer cells (see Georges Dec. ¶¶ 10 and 11). In addition, the size of MDA-MB-231 human breast cancer cell line xenografts was decreased as compared to taxol only treatments, again indicating that anti-vimentin antibody treatment was enhancing the taxol treatment (see Georges Dec. ¶ 12). Thus, ^{131}I-labeled anti-vimentin antibodies improve taxol treatments *in vivo* by binding to cell-surface-expressed vimentin.

The data proves that ^{131}I-labeled anti-vimentin antibodies bind to cell-surface-expressed vimentin *in vivo* (see Georges Dec. ¶¶ 10-13). This is apparent because *in vitro* data from cells transiently expressing increased levels of vimentin shows that tumor cells express increasing levels of vimentin on the cell surface (see Georges Dec. ¶ 9 and ¶ 13; discussing Fig. 1). The monoclonal antibody used in the *in vivo* experiments binds specifically to vimentin, and only bind to cell-surface-expressed vimentin in these experiments because antibodies, due to their size, do not cross the cell membrane into the cytosol with any appreciable efficiency (see Georges Dec. ¶ 8). In short, any improved inhibitory effects of taxol mediated by the radiolabeled anti-vimentin antibodies are due to those antibodies binding to vimentin expressed on the surface of cancer cells (see Georges Dec. ¶¶ 7, and 10-13).

For all of these reasons, the improved treatment results shown in the taxol and anti-vimentin combination therapy group establishes that the radiolabeled anti-vimentin antibodies bound to the surface of the tumor cells *in vivo,* thereby finding and identifying the cell-surface-expressed vimentin target in the chemical milieu of the organism.

Furthermore, such experiments establish that vimentin binding agents—including antibodies, modified LDL, NLK1 protein, vimentin, desmin, glial fibrillary acidic protein, peripherin, fimbrin, RhoA-binding kinase alpha, and protein phosphatase 2A—can bind to cell-

surface-expressed vimentin *in vivo* (see Georges Dec. ¶¶ 14-16). Applicants have tested one of the monoclonal antibody for its ability to bind to vimentin in a subject, and the targeting agent specifically bound to cell-surface-expressed vimentin. The other vimentin binding agents are known in the art to bind vimentin, thus the teachings of the specification combined with the knowledge in the art enable the use of *all* vimentin binding agents because the other members of the species all share the characteristic of *binding to vimentin* (see Georges Dec. ¶ 14). For instance, modified LDL is a known binding agent of vimentin, and binds to vimentin with high specificity (see Specification, paragraph [0194], citing, Heidenthal, *et al.* (2000) *Biochem. Biophys. Res. Comm*. 267: 49-53). With this knowledge and the teachings of the specification, one of ordinary skill in the art could utilize modified LDL as vimentin targeting agent. Furthermore, the data provided herewith shows that vimentin targeting agents would bind *in vivo* to cell-surface-expressed vimentin (see Georges Dec. ¶ 16). Therefore, those of ordinary skill in the art are enabled to practice the full scope of the claimed invention, including *in vivo* detection using vimentin targeting agents, without undue experimentation.

Accordingly, Applicants respectfully request that this enablement rejection of independent claims 10 and 66, and dependent claims 12, 14-19, 68, and 70-74 be reconsidered and withdrawn.

CONCLUSIONS

In view of the arguments set forth above, Applicants respectfully submit that the outstanding rejections contained in the Office Action mailed on August 13, 2007 should be reconsidered and withdrawn.

The time for responding to this action has been extended to February 13, 2008 by the accompanying Petition for a Three Month Extension of Time and payment of fee. No additional fees are believed to be due in connection with this response. However, please charge any underpayments or credit any overpayments to Deposit Account No. 08-0219.

If the Examiner believes that any further discussion of this communication would be helpful, please contact the undersigned at the telephone number provided below.

Respectfully submitted,

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